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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,867	09/16/2005	Tanya Kathleen Church	270851US0PCT	5987

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
02/17/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/531,867	CHURCH ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 12-14, 16-27* is/are pending in the application.

4a) Of the above claim(s) *18-22 and 26-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 12-14, 16-17, and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 12-14, and 16-27 are pending. The notice of allowance mailed on January 6, 2011 is vacated in view of the new rejections set forth below. Prosecution is re-opened. Applicants amended claims 1, 16, and 23-25 in the claim set submitted on December 17, 2010. Applicants newly introduced claims 23-27 in the claim set submitted on December 14, 2010. Claims 18-22 and 26-27 are withdrawn from consideration. **Claims 1-9, 12-14, 16-17, and 23-25 are under consideration** in the instant office action. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Election/Restrictions

Because the January 6, 2011 notice of allowance is vacated, the restriction requirement, originally set forth in the August 17, 2009 office action is reinstated. Therefore, claims 18-22 and 26-27 are withdrawn from consideration at this time per the restriction requirement of record.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 5-8, 12, 14, and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Lewis et al. (WO 01/89480).

Applicants claim a pharmaceutical solution aerosol formulation which consists of (i) salmeterol, a stereoisomer thereof, or a physiologically acceptable salt thereof, (ii) optionally a

corticosteroid, (iii) optionally an anticholinergic atropine-like compound, and (iv) a propellant system consisting of (a) liquefied HFA propellant, (b) co-solvent, (c) a mineral acid, and (d) 0-5% w/w water, wherein said cosolvent is present in an amount of no more than 35% w/w based on the total weight of said formulation, said formulation has a pH of 2.5-5.5, and said pH has been adjusted by addition of said mineral acid.

Lewis discloses **aerosol solution compositions** for use in an inhaler comprising **(i) an active material, (ii) a small amount of a mineral acid to stabilize the composition, and (iii) a propellant system containing (a) a hydrofluoroalkane, (b) a cosolvent**, and (c) optionally a low volatility component (e.g. abstract, pg. 3, lines 3-10, and claim 1). The formulation stability is also promoted by containing the formulations in a suitable can having part or all of its internal metallic surfaces made of stainless steel, anodized aluminum, or lined with an inert organic coating (abstract, pg. 7, lines 11-12, claim 10). **Suitable active agents are disclosed to be short and long-acting beta-2 adrenergic agonists, such as salbutamol, formoterol, salmeterol, TA 2005, salt [sic] thereof and their combinations with steroids, such as, beclomethasone dipropionate, fluticasone propionate, budesonide and its 22-R epimer** (pg 7, lines 4-8 and claim 9). Beclomethasone dipropionate, fluticasone propionate, and budesonide and its 22-R epimer are corticosteroids. **Salmeterol xinafoate is disclosed** as being known in the prior art (pg. 6, line 10). Salmeterol xinafoate is a known salmeterol salt. **Ethanol is disclosed as being the preferred cosolvent** (pg. 7, line 20). **The hydrofluoroalkane propellant is preferably HFA 134a, HFA 227, and mixtures thereof** (pg. 7, lines 18-19 and claim 8). Lewis does not exemplify any formulations containing salmeterol. Lewis discloses formulations containing ethanol in amounts of 12% w/w (pg. 4, line 17; Example 5 at pg. 13, line 4; and Table 5 on page

15), 10-20% w/w (Ex. 1 at pg. 8, lines 14-15), 15% w/w (Example 2 at pg. 9, line 21), and 20% w/w (Example 3 at pg. 11, line 10; Example 4 at page 11, line 25; and Table 4 on pg. 12).

Lewis **discloses a method of filling a pressurized metered dose inhaler comprising (a) preparing a solution of one or more active ingredients in one or more co-solvents, optionally containing an appropriate amount of a low volatility component; (b) filling the device with said solution; (c) adding a pre-determined amount of a strong mineral acid; (d) adding a propellant containing a hydrofluoroalkane (HFA); and (e) crimping with valves and gassing** (pg. 6, line 25 through pg. 7, line 3 and claim 11).

It is the Examiner's position that an ordinary skilled artisan, based on Lewis' disclosures, could clearly envisage a pharmaceutical aerosol formulation consisting of (i) salmeterol, a stereoisomer thereof, or a physiologically acceptable salt thereof, (ii) optionally a corticosteroid, and (iii) a propellant system consisting of (a) liquefied HFA propellant, (b) co-solvent, (c) a mineral acid, and (d) 0 % w/w water, wherein said cosolvent is present in an amount of no more than 35% w/w based on the total weight of said formulation, said formulation has a pH of 2.5-5.5, because Lewis does not add any water to the disclosed formulations and the only amounts of ethanol co-solvent mentioned in Lewis' disclosure are all well below the 35% maximum co-solvent amount recited in Applicants' claims. Because low volatility components are optional in the prior art formulations and Lewis' disclosures permit the ordinary skilled artisan to clearly envisage the claimed formulations, it is concluded that the envisaged formulations must inherently exhibit the same properties recited in Applicants' claims 6-7.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-9, 12, 14, 16, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (WO 01/89480) and Meade et al. (US 2006/0057074).

Applicant Claims

Applicants claim (1) a pharmaceutical solution aerosol formulation, as described above, comprising an anticholinergic compound or having a salmeterol xinafoate concentration of 0.005 to 15% w/v and (2) a method of preparing a pharmaceutical formulation.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lewis are set forth above.

Meade teaches **pharmaceutical compositions comprising anticholinergics, betamimetics, and corticosteroids that are suitable for the treatment of respiratory diseases (abstract) and which exhibit a synergistic therapeutic effect** [0003]. Preferred betamimetics are salmeterol and formoterol salts [0011]. **Suitable anticholinergics include tiotropium bromide, ipratropium bromide, oxitropium bromide**, and other pharmaceutically acceptable salts of tiotropium ipratropium, and oxitropium [0006]. **Suitable corticosteroids include beclomethasone, budesonide**, fluticasone, mometasone, etc. [0007]. **Preferred salmeterol salts are salmeterol xinafoate and salmeterol hemi-hydrogen sulfate** [0013]. The formulations may be formulated as **propellant-containing aerosols, wherein the three active substances may be dissolved**, dispersed, or in combinations thereof (e.g. one active may be dissolved while the other two actives are dispersed or all three actives are dissolved). Particularly preferred propellants include **TG134a (i.e. HFA 134a), TG227 (i.e. HFA 227), and mixtures thereof** [0041]. The inhalation aerosols **may contain up to 5% w/w of each of the three active substances, for example, 0.002-5% w/w of each active substance** [0043].

Russell teaches a metered dose inhaler (MDI) for salmeterol comprising an exit channel whose diameter at its narrowest is between 0.2 and 0.4 mm (abstract). Russell teaches that a **MDI typically comprises a channeling device which may comprise an actuating device for the valve** (pp 4, lines 14-23).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lewis lacks the teaching of formulations comprising both salmeterol and an anticholinergic. This deficiency is cured by the teachings of Meade. Lewis does not anticipate claim 16, because Lewis teaches a method wherein the recited steps (b)-(f) of instant claim 16 are performed in a different order. Lewis' teachings nonetheless render claim 16 obvious as explained below.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill at the time of the instant invention to modify the teachings of Lewis to add anticholinergics to Lewis' formulations comprising salmeterol, because the combination of an anticholinergic, corticosteroid, and betamimetic (e.g. salmeterol) results in synergistic therapeutic effects (Meade). An ordinary skilled artisan would have been motivated to combine the references with a reasonable expectation of success, because both references teach solution aerosol formulations comprising HFA propellants and Meade teaches that the combination of an anticholinergic, corticosteroid, and betamimetic (e.g. salmeterol) results in synergistic therapeutic effects.

Regarding the method of claim 16 of the instant application, Lewis teaches the same steps, but in a different order. Step (b) of claim 16 of the instant application is accomplished by Lewis' step of adding acid (Lewis step c). It is the Examiner's position that addition of the mineral acid after filling the device, but prior to adding the propellant, does not result in a material change in the composition contained within the device, with the exception of the intended change of making the formulation have an acidic pH value. Thus, the order of the steps recited in Applicants' claim 16, absent evidence to the contrary, is considered to be non-critical. As a result an ordinary skilled artisan would find the method of instant claim 16 prima facie obvious over the teachings of Lewis. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (WO 01/89480) and Meade et al. (US 2006/0057074) as applied to claims 1-3, 5-9, 12, 14, 16, and 23-25 above, and further in view of Cripps et al. (US 2005/0048001) (of record).

Applicant Claims

Applicants claim a method of preparing a pharmaceutical formulation wherein the device has a valve actuator diameter of 0.22 mm.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lewis and Meade are set forth above.

Cripps is provided only to establish that metered dose inhalers comprising a valve actuator having an exit orifice diameter of less than 0.25 mm were conventionally used in the art at the time of the instant invention. The valve actuator having an exit orifice diameter overlaps with the valve actuator orifice diameter recited in Applicants' claim 17.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lewis lacks the teaching of a method of preparing a pharmaceutical formulation wherein the device that is filled comprises a valve actuator with a diameter that is 0.22 mm. This deficiency is cured by the teachings of Cripps.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill at the time of the instant invention to use a MDI comprising a channeling device having a valve actuator orifice diameter of 0.22 mm, because it was conventional in the art at the time of the instant invention to use said channeling devices. An ordinary skilled artisan would have been motivated to use a channeling device having a valve actuator orifice diameter of 0.22 mm with a reasonable expectation of success, because such channeling devices were conventionally used and would reasonably be expected to be readily available. Moreover, the recited valve actuator orifice is prima facie obvious because the prior art teaches an overlapping and encompassing valve actuator orifice diameter. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 4 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (WO 01/89480) and Meade et al. (US 2006/0057074) as applied to claims 1-3, 5-9, 12, 14, 16, and 23-25 above, and further in view of Bozung et al. (US 2002/0189610).

Applicant Claims

Applicants claim a pharmaceutical solution aerosol formulation, as described above, wherein the composition comprises specific amounts of salmeterol (i.e. 0.04% w/w [claim 13]), ethanol (i.e. less than or equal to 25% w/w [claim 4] or 15% w/w [claim 13]), and water (i.e. 0.5% to 5% w/w [claim 4] or 2% w/w [claim 13]).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lewis and Meade are set forth above.

Bozung establishes that solution formulations containing both salmeterol and ipratropium bromide are known (e.g. [0117]-[0121]) and that mixtures of water and ethanol may be used [0071].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lewis lacks the teaching of a pharmaceutical solution formulation of salmeterol containing water. This deficiency is cured by the teachings of Bozung.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill at the time of the instant invention that one could successfully obtain HFA solutions formulations of salmeterol containing small amounts of water, because the prior art establishes that aqueous ethanolic solutions of salmeterol and its physiologically acceptable salts may be successfully obtained (Bozung). From the knowledge of prior art aqueous/ethanolic solution formulations of salmeterol, the ordinary skilled artisan would reasonably infer that the presence of water in HFA solution formulations would not be detrimental to the stability of the composition or to the stability of the dissolved salmeterol contained therein. An ordinary skilled artisan would have had a reasonable expectation of combining the teachings of Lewis, Meade, and Bozung, because all these references teach solution formulations of salmeterol in combination with one or more additional active agents, wherein the formulations also comprise an acid (e.g. HCl) and are acidic. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Conclusion

Claims 1-9, 12-14, 16-17, and 23-25 are rejected. Claims 18-22 and 26-27 are withdrawn from consideration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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